Amendments to the Specification:

Please replace the paragraph beginning at page 7, line 14, with the following rewritten paragraph:

--The compounds of the invention contain at least one halogen that can be radioisotopic. Of particular interest are the radioisotopes ^{18}F, ^{123}I, ^{125}I, ^{131}I, ^{75}Br, ^{76}Br, ^{77}Br, and ^{82}Br. For compounds having two halogens, alternative syntheses have been devised to permit rapid substitution of an isotopic halogen at a late step. The same component, for example FEINT, can be synthesized with either ^{123}I or ^{18}F, using late step syntheses that permit high radiochemical yield and maximize usable product life.--

Please replace the paragraph beginning at page 8, line 31, with the following rewritten paragraph:

--"Z isomer" as used herein refers to a conformation of alkenes in which two substituents with higher atomic numbers on each alkene carbon are on the same side of the double bond. For example, Z isomer of ZIENT refers to the structure in which ~~has~~ the phenyl ring and iodine are on the same side of the double bond of phenyl-CH=CHI.--

Please replace the paragraph beginning at page 9, line 13, with the following rewritten paragraph:

--Preferred compounds of the invention exemplified are 2β-carbomethoxy-3β-(4-(2-Z-iodoethenyl-phenyl)nortropane (ZIENT), 2β-carbomethoxy-3-β-(4-(2-fluoroethyl)-3-iodophenyl)nortropane (FEINT), 2β-carbomethoxy-3β-(4-(2-fluoroethyl)-3-bromophenyl)nortropane (FEBrNT) and N-methyl and N-fluoroethyl-derivatives of ZIENT, FEINT, ~~FIENT,~~ and FEBrNT. When labeled with the single photon-emitting radioisotope

iodine-123 or the positron-emitting radioisotope fluorine -18, these compounds can be used as a diagnostic imaging agent to measure central nervous system (CNS) neuronal function in the brain of patients suffering from major depression, obsessive compulsive disorder and cocaine addiction. These tropanes were designed to bind with high affinity to the serotonin transporter (SERT). Radiolabeled ZIENT, FEINT and FEBrNT analogs are excellent candidate diagnostic radiopharmaceuticals for differentiating depression from other psychiatric disorders and assisting in the management of treatment of depression. Radiolabeled ZIENT, FEINT and FEBrNT may also be valuable radiopharmaceuticals for assisting in the management of treatment of cocaine addiction.--

Please replace the paragraph beginning at page 9, line 28, with the following rewritten paragraph:

--Unique characteristics of these radiopharmaceuticals are incorporation of iodine-123 directly on a phenyl ring or as a Z-iodoethenyl group attached to a phenyl group or the attachment of fluorine-18 to a fluoroethyl substituted phenyl ring. These groups were found to be stable to metabolism and *in vivo* loss of the fluorine-18 and iodine-123 radioisotope. This allows labeling with either fluorine-18 or iodine-123 which gives rise to radiopharmaceuticals that can be used with either positron emission tomography (PET) or single photon emission (SPECT) imaging modalities. *In vitro* binding studies with FEINT, FEBrNT, FECINT, and ZIENT are shown in Table 1. ~~In~~ *In vitro* binding studies in cells stably transfected with human SERT using [^{3}H]citalopram afforded Ki (nM) of 0.1, for the dopamine transporter (DAT) in cells stably transfected with human DAT using [^{3}H] WIN35,428 afforded Ki (nM) of 42.4 and for the norepenephrine transporter (NET) in cells stably transfected with human NET using [^{3}H] Nisoxetine afforded Ki (nM) of 64.9 for FEINT. Thus, FEINT was found to be selective and possess a high affinity for SERT with a low affinity for DAT (DAT/SERT=424) and NET (NET/SERT=649). *In vitro* binding studies with FEBrNT in cells stably transfected with human SERT using [^{3}H]citalopram afforded Ki (nM) of 0.22, for the dopamine transporter

(DAT) in cells stably transfected with human DAT using [^{3}H] WIN 35,428 afforded Ki (nM) of 23.2 and for the norepenephrine transporter (NET) in cells stably transfected with human NET using [^{3}H] Nisoxetine afforded Ki (nM) of 126 for FEBrNT. Thus, FEBrNT was found to be selective and possess a high affinity for SERT with a low affinity for DAT (DAT/SERT=100) and NET (NET/SERT=573). ~~In~~ *In vitro* binding studies in cells stably transfected with human SERT using [^{3}H]citalopram afforded Ki (nM) of 0.56, for the dopamine transporter (DAT) in cells stably transfected with human DAT using [^{3}H] WIN35,428 afforded Ki (nM) of 27 and for the norepenephrine transporter (NET) in cells stably transfected with human NET using [^{3}H] Nisoxetine afforded Ki (nM) of 117 for FECINT. Thus, FECINT was found to be selective and possess a high affinity for SERT with a low affinity for DAT (DAT/SERT=48) and NET (NET/SERT=209). [^{18}F]FEINT and [^{18}F]FEBrNT were incubated with pig tailed macaque coronal brain slices and the slices ~~apposed~~ exposed to film for 30 min. Binding was localized to the thalamus, hypothalamus, caudate, putamen and temporal cortex. Incubation of the brain slices with [^{18}F]FEINT (Fig.1) and [^{18}F]FEBrNT and 10 uM citalopram yielded maximal inhibition (90%) of binding. These results suggest that [^{18}F]FEINT and [^{18}F]FEBrNT are excellent candidates for *in vivo* primate studies for mapping SERT sites.--

Please replace the paragraph beginning on page 10, line 28 with the following rewritten paragraph:

--*In vitro* binding studies with ZIENT in cells stably transfected with human SERT using [^{3}H]citalopram afforded Ki (nM) of 0.031, for the dopamine transporter (DAT) in cells stably transfected with human DAT using [^{3}H] WIN 35,428 afforded Ki (nM) of 3.47 and for the norepenephrine transporter (NET) in cells stably transfected with human NET using [^{3}H] Nisoxetine afforded Ki (nM) of 15 for ZIENT. Thus, ZIENT was found to be selective and possess a high affinity for SERT with a low affinity for DAT (DAT/SERT=100) and NET (NET/SERT=484). ~~(NET/SERT=484).~~ The distribution of radioactivity expressed as percent

dose per gram in tissues of unfasted male Sprague Dawley rats at 60 min and 120 min after intravenous administration of ~~[^{123}I] ZIENT.~~ [^{123}I] ZIENT showed the greatest accumulation in brain regions rich in serotonergic neurons with greater hypothalmus to cerebellum ratios of 3 to 1 and 5 to 1 at 60 and 120 min post injection respectively and prefrontal cortex to cerebellum ratios of 2.9 to 1 at ~~and~~ 120 min post injection. A [^{123}I] ZIENT SPECT brain imaging study in a rhesus money demonstrated high [^{123}I] ZIENT uptake in the midbrain by 54 min post injection. In an equilibrium displacement experiment with fluvoxamine (5mg) in a rhesus monkey, radioactivity in the midbrain was significantly displaced by 35 min post i.v. injection. These data demonstrate that ZIENT labeled with ^{123}I is a potential radiopharmaceutical for the diagnosis and management of treatment of psychiatric disorders such as depression and obsessive-compulsive disorder in humans using emission tomographic techniques.--

Please replace the paragraph beginning at page 12, line 11, with the following:

--Recently, it was reported that replacement of the 3β-(4-iodophenyl) group of 2β-carbomethoxy-3β-(4-iodophenyl)nortropane (nor-CIT) with a 3β-(4-ethyl-3-iodophenyl) group afforded the analog (EINT) which was found to show subnanomolar affinity for the SERT (IC_{50}=0.69 nM vs [^{3}H]WIN 35428) and to be 500 times more selective for the SERT than the dopamine transporter (DAT) (IC_{50}=329 nM vs [^{3}H]paroxetine) [Blough, B.E. *et al.* (1997) *J. Med. Chem.* **40**:3861]. This suggested to us that the 3β-4' ethylphenyl substituent could allow introduction of sulfonyl esters for ~~incorporationg~~ incorporating fluorine-18 as 4'-[^{18}F] fluoroethyl group. Therefore, several new radioligand bioisosteres of EINT: 2β-carbomethoxy-3β-(4-(2-fluoroethyl)-3-iodophenyl)nortropane (FEINT, **10a**), 2β-carbomethoxy-3β-(4-3-fluoropropyl)-3-iodophenyl)nortropane (FPINT, **10b**) and ~~2ββcarbomethoxy-~~2β-carbomethoxy-3β-(4-(2-fluoroethyl)-3-bromophenyl)nortropane (FEBrNT, **12a**) and 2β- carbomethoxy-3β-(4-(2-fluoroethyl)-3-~~chloroophenyl~~ chlorophenyl)nortropane (FEClNT, **14a** ~~12b~~) were synthesized as potential PET and SPECT

SERT imaging agents that could be labeled with either fluorine-18, ~~bromine 75, 76, carbon 11~~ bromine -75, -76, carbon -11 or iodine-123.--

Please replace the paragraph beginning at page12, line 26, with the following:

--Scheme 1 provides exemplary synthetic routes for the preferred compounds of the invention, e.g. FEINT, FPINT, FEBrNT and FEClNT. Modification of the materials and methods can be made by routine choice and without undue experimentation by those skilled in the art. The preparation of analogues 10a,b involved a seven step sequence of reactions. In this synthetic approach methyl anhydroecgonine was treated with a 4-trimethylsilylphenylmagnesium bromide to give the corresponding 2β-carbomethoxy-3β-(~~4-trimethylsilyphenyl~~ 4-trimethylsilylphenyl)tropane (2). The tropane 2 was treated with bromine monochloride followed by vinyltributyltin ~~vinyltribytyltin~~ and allyltributyltin to ~~tro~~ afford 4a and 4b respectively. Tropanes 4a and 4b were converted to their corresponding ω-alcohols followed by reaction with I_2 to give 3β-4'-(ω-acetoxylalkyl)-3'-iodophenyltropanes 6a and b. Tropanes 6a and 6b were treated with ~~TrocCl/HCl~~ TrocCl/HCl MeOH followed by DAST and Zn to form the corresponding nortropanes FEINT (10a) and FPINT (10b). FEBrNT (12a) and FEClNT (~~12b~~ 14a) were prepared in a five-step reaction sequence from 6a by conversion to 3β-4'- (2-acetoxyethyl)-3'-bromophenyltropane and to 3β-4'-(2-acetoxyethyl)-3'-~~hchlorophenyltropane~~ chlorophenyltropane respectively, followed by desmethylation and fluorination as described for 10a.--

Please replace the paragraph beginning at page 16, line 30, with the following:

--The long-lived isotopes, such as ^{123}I with a half-life of 13 hours, are commercially available from sources such as Nordion International Ltd. (Vancouver, B.C., Canada) ~~((Vancouver, B.C., Canada)~~ or NEN/DuPont (N. Billerica, MA). Shorter-lived isotopes, such as ^{18}F can be obtained from a regional source, within ~~with~~ a ~200 mile radius of the site of intended use.--

Please replace the paragraph beginning at page 18, line 14, with the following:

--Studies by Blough, et al., [~~Bough~~ Blough, et al. (1996) *J. Med. Chem.* **39**(20):4027-35] indicated that introduction of isopropenyl and *cis*-propenyl substituents at the 4'-position of the 3β-phenyl ring afforded the analogs with affinity and specificity for SERT. 2β-carbomethoxy-3β-(4'-isopropenylphenyl)nortropane (nor-β-CIPPT) and 2β- carbomethoxy-3β-(4'*cis*-propenylphenyl)notropane (nor-β-CCPPT) were found to be the most potent alkenyl analogs. Nor-β-CIPPT showed subnanomolar affinity for the SERT (IC_{50}=0.6 nM vs [^{3}H]paroxetine) and ~~to be~~ was 38 times more selective for the SERT than the dopamine transporter (DAT) (IC_{50}=23 nM vs [^{3}H]WIN 35428). Nor-β-CCPPT possessed lower affinity for the SERT (IC_{50}=1.15 nM vs [^{3}H]paroxetine) and was found to be 28 times more selective for the SERT than the dopamine transporter (DAT) (IC_{50}=32 nM vs [^{3}H]WIN 35428). These studies strongly suggest that the incorporation of fluorine and iodine at a 4'-isopropene, *cis*-propene and vinyl substituent at the 4'-position of the 3β-phenyl ring can lead to a potent SERT ligand. Thus, several new halogen bioisosteres of nor-β-CIPPT and nor-β-CCPPT, e.g. 2β-carbomethoxy-3β-4'-(Z-2-iodoethenyl)phenyl)nortropane (ZIENT), 2β-carbomethoxy-3β-(4'(Z-3-fluoropropenyl)phenyl)-nortropane (ZFPPNT) and 2β-carbomethoxy-3β-4'-(2-fluoroisopropenyl)phenyl)nortropane (FIPPNT) were synthesized, as potential PET and SPECT SERT imaging agents that could be labeled with either fluorine-18, carbon-11 or iodine-123.--

Please replace the paragraph beginning at page 19, line 1, with the following:

--Schemes 2-4 provide exemplary synthetic routes for the preferred compounds of the invention, e.g. ZEINT, ZFPPNT and FIPPNT. The preparation of ZIENT involved a five-step sequence of reactions (Scheme 2). In this synthetic approach 2β-carbomethoxy-3β-4('-bromophenyl)nortropane was treated with vinyltributyltin to yield ~~vinyltribytyltin to~~ 2β-carbomethoxy -3β-(4'-ethenylphenyl)nortropane. The N-Boc vinylnortropane derivative was converted to the ~~N-Boc 2β-carbomethoxy-3β-4'-formylphenyl)nortropane~~ N-Boc 2β-

carbomethoxy-3β-(4'-formylphenyl)nortropane followed by reaction with triphenyl-phosphoniumiodomethyne yllide and removal of the N-Boc group to give ZIENT.--

Please replace the paragraph beginning at page 21, line 19, with the following:

--A radiosynthetic method for [^{123}I]ZIENT was developed to evaluate its regional *in vivo* brain distribution. This radiosynthesis employed a trimethyltin ~~trimethytltin~~ substrate (Scheme 2). The tin precursor was treated with 14.5 mCi NCA [^{123}I]NaI and 3% H_2O_2 in ethanolic HCl ~~HCl~~. HPLC purification on a Waters C_{18} RP 8mm, 80:20:0.1 CH_3OH:H_2O:NEt_3, flow rate 1 mL/min afforded 8.5 mCi [^{123}I]ZIENT, 69% radiochemical yield E.O.B. in a total synthesis time of 360 min with a specific activity of 1700 mCi/μmol.--

Please replace the paragraph beginning at page 22, line 32, with the following:

--SPECT data acquired with the CERASPECT camera had a resolution in all three axes of approximately 12 mm full width half-maximum measured using a ^{123}I line source and 20 cm water-filled cylindrical phantom that was reconstructed using a cutoff of 1 cm. The baboon was injected with 10 mCi of [^{123}I]ZIENT and serial images (128 x 128 x 64 matrix: pixel size = 1.67 x 1.67 mm, slice, thickness = 1.67 mm, voxel volume = 4.66 mm^3) ~~were acquired at 159 1.67 x 1.67 mm, slice thickness = 1.67 nm, voxel volume = 4.66 mm^3)~~ were acquired at 159 keV, in step and shoot mode at 10 min each for a total of 360 to 390 min and 32 to 35 acquisitions per experiment. Images were reconstructed using a ramp and a Butterworth filter (cutoff = 0.65 cm- power factor = 10). To identify brain regions, MRI scans of 1.5 mm contiguous slices were obtained with a 1.5 Tesla GE Signa device. Axial images were acquired using a spoiled GRASS (~~gradiant~~ gradient recall acquisition in the steady state) sequence with TR = 25ms, TE = 5 ms, NEX = 2, matrix = 256 x 192, field of view = 16cm. The diancephalon, ~~diencepalon~~, superior and inferior brainstem and striatum were the regions of highest uptake in the brain and showed clear visualization at 300-360 min after

injection (Figure 6). The regional uptake of [^{123}I]ZIENT in the brain of an anesthetized baboon is shown in Figure 7. The uptake ratio of brainstem/cerebellum was 3.0:1 at 300-360 min.--

Please replace the paragraph beginning at page 23, line 22, with the following:

--In order to determine whether any structural modifications of ~~on~~ ZIENT, FEINT, ~~FIENT,~~ and FEBrNT ~~FIBrNT~~ would still yield high selectivity and specificity for SERT similar to the results seen with ZIENT, FEINT, FEBrNT and FEClNT, various substitutions on the tropane nitrogen and the 2-beta carboxyester position were made and tested in *in vitro* binding studies.
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Please replace the paragraph beginning at page 24, line 5, with the following:

--Scheme 5 provides exemplary synthetic route for 2β-carbomethoxy-3β-4'-(Z-2-iodoethenyl)phenyl)tropane ~~(ZIET)and~~ (ZIET) and [^{123}I] ZIET. The preparation of ZIET involved a five-step sequence of reactions. In this synthetic approach ~~2β-carbomethoxy-3β-4(' bromophenyl)tropane~~ 2β-carbomethoxy-3β-(4'-bromophenyl)tropane was treated with vinyltributyltin to yield ~~vinyltribytyltin to~~ 2β-carbomethoxy -3β-(4'-ethenylphenyl)tropane. The vinyltropane derivative was converted to ~~2β-carbomethoxy-3β-4'-formylphenyl)tropane~~ 2β-carbomethoxy-3β-(4'-formylphenyl)tropane followed by reaction with triphenyl-phosphoniumiodomethyne yllide to give ZIET.--

Please replace the paragraph beginning at page 25, line 1, with the following:

--Scheme 6 provides exemplary synthetic route for ~~2β-carbo-ω-fluoroalkoxy-3β-4'-(Z-2-haloethenyl)phenyl)tropanes~~ 2β-carbo-ω-fluoroalkoxy-3β-4'-(Z-2-haloethenylphenyl)tropanes. The preparation of ~~2β-carbo-ω-fluoralkoxy~~ 2β-carbo-ω-fluoroalkoxy derivatives of ZIET will involve a seven-step sequence of reactions. In this synthetic approach ecogine will be treated

with phosphorous oxychloride followed by the appropriate fluoroalcohol or benzyloxyalcohol to the corresponding anhydroecognine ω-fluoroalkyl- and ω-benzyloxyalkyl- esters. The esters will undergo Michael addition with 4-trimethylsilylmagnesium bromide followed by bromine to give the corresponding 2β-carbo-ω-fluoroalkoxy-3β-4'-(bromophenyl)tropanes and 2β-carbo-ω-benzyloxyalkoxy-3β-4'-(bromophenyl)tropanes. The 4-bromophenyltropanes will be treated with vinyltributyltin ~~vinyltribytyltin~~ to give the corresponding ~~2β-carbo-ω-fluoralkoxy-3β-(4'-ethenylphenyl)tropanes~~ 2β-carbo-ω-fluoroalkoxy-3β-(4'-ethenylphenyl)tropanes and 2β-carbo-ω- benzyloxyalkyl -3β-(4'-ethenylphenyl)tropanes. The vinyltropane derivatives will be converted to ~~2β-carbomethoxy-3β-4'-formylphenyl)tropane~~ 2β-carbomethoxy-3β-(4'-formylphenyl)tropane followed by reaction with triphenyl-phosphoniumiodomethyne yllide to give the ~~2β-carbo-ω-fluoralkoxy- 2β-carbo-ω-benzyloxyalkoxy~~ 2β-carbo-ω-fluoroalkoxy- 2β-carbo-ω-benzyloxyalkoxy derivatives of ZIET.--